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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,395	01/22/2004	Tony Giordano	26788-009	4861

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POTTER ANDERSON & CORROON LLP
ATTN: KATHLEEN W. GEIGER, ESQ.
P.O. BOX 951
WILMINGTON, DE 19899-0951

EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,395	GIORDANO ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 76-140 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 76-103, drawn to a method for down regulating gene expression using a double stranded RNA, classified variously, for example, in class 435, subclass 455 depending on the nature of method steps used to effectuate the result.

II. Claims 104-114, drawn to a method of screening a double stranded RNA delivery complex formulation so as to minimize cytotoxicity associated with delivery of a double stranded RNA of interest, classified variously in class 506, subclass 12.

III. Claims 115-140, drawn to a method for identifying a double stranded RNA that modulates a function in a vertebrate cell, classified variously in class 506, subclass 2.

2. The inventions are distinct, each from the other because of the following reasons:

3. Inventions I and II are directed to related methods. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, mode of operation, function, or effect because Group II is drawn to minimizing cytotoxicity associated with the delivery of double stranded RNA, which requires a delivery agent at two or more different positive/negative ratios. This is not the case for Group I.

Furthermore, Group I requires a vector, which is not the case for Group II. In addition, the effect of Group I is to down regulate a gene whereas the effect of Group II is to screen for agents that will minimize toxicity. Consequently, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

4. Inventions I and III are directed to related methods. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, mode of operation, function, or effect because Group III is drawn to a process for identifying a double stranded RNA that modulates a function in a vertebrate cell using a library of unknown dsRNA that becomes integrated into the host genome whereas Group I requires instead the use of a single double stranded RNA vector that has already been identified for down regulating gene expression that may or may not integrate into the host genome. In addition, the methods have different effects. Group III results in the "identification" of a single dsRNA from the library that "modulates" presumably either by "up regulating" or "down regulating" a gene whereas Group III results only in the "down regulation" of a gene without the need for its identification. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

5. Inventions II and III are directed to related methods. The related inventions are distinct if

the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed have a materially different design, mode of operation, function, or effect because Group II is drawn to minimizing cytotoxicity associated with the delivery of double stranded RNA using a positively charged delivery agent, which is not the case for Group III. Group III is drawn, instead, to the identification of a dsRNA that modulate the function of a cell that has been transfected with an episomal vector containing said cells. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

6. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;
(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
(d) the prior art applicable to one invention would not likely be applicable to another invention;
(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention may be made with or without traverse. To reserve a right to

petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

7. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined

claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Additional Species Election

8. This application contains claims directed to patentably distinct species of the claimed invention for Groups I-IV. Election is required as follows.

Group I

9. If applicant elects the invention of Group I, applicant is required to elect from the following patentably distinct species. Claim 1 is generic.

Subgroup 1: Species of monitoring RNA stress response (e.g., see claim 76 and 102)

Applicant must elect, for the purposes of search, a ***single species*** of monitoring RNA stress response such as apoptosis (see claim 102). Other examples include measuring interferon induction 2'5' OAS activiation/induction, PKR induction/activation, anti-proliferative response, etc (e.g., see specification, page 36, last paragraph). Applicants must further elect a specific assay for monitoring the above phenotypes such as TUNEL assay, ELISA assay, etc. (e.g., see specification, page 36, last paragraph; see also claims 92, 93, 94, 95, etc). Please be as specific as possible. Electing a general class will be

held non-responsive. For example, electing detecting an RNA stress response using a microscope to look for one or more cytopathic effects (see claim 99) would be held non-responsive because the general class of cytopathic effects could be elected with greater specificity to include detached cells, rounded cells, etc (see claim 100). Likewise, electing the general class of apoptosis assay would be held to be non-responsive because this general class could be elected with greater specificity to cinlude Annexin V staining, propidium iodide staining, DNA laddering, etc (see claim 103).

Subgroup 2: Species of target gene and method for monitoring (e.g., see claim 76, 79, 80)

Applicant must elect, for the purposes of search, a ***single species*** of target gene including whether said gene is endogenous, pathogenic, etc (see claims 79 and 80). Applicants must also elect a method for monitoring said target gene such as by measuring a decrease in the level of the protein by the use of ELISA, Western blot, reporter gene activity via the use of β-galactosidase, green fluorescent protein, luciferase activity, RT-PCR with "housekeeping" function, etc (e.g., see specification, page 30, last paragraph).

Subgroup 3: Species of vector (e.g., see claim 76)

Applicant must elect, for the purposes of search, a ***single species*** of vector including whether it is integrated or non-integrated (e.g., see specification, page 5, last paragraph). Applicants must further indicate whether said vector contains an operably linker promoter and, if so, elect a specific species of said promoter such as HCMV-ID, SCMV, etc. (e.g., see specification, page 5, last paragraph). Please be a specific as possible. Applicants must also elect a specific marker such as hygromycin, G418, etc if present (e.g., see specification, page 14, paragraph 1; see also page 9, paragraph 1). Finally, Applicants must also elect a specific reporter gene if present such as GFP, luciferase, etc (e.g., see specification, page 9, paragraph 1; see also page 31, last paragraph).

Subgroup 4: Species of cell (e.g., see claim 76)

Applicant must elect, for the purposes of search, a ***single species*** of cell such as human cancer cell, stem cell, neuronal cell, etc. (e.g., see specification, page 8, paragraph 2). Please be a specific as possible (e.g., "human cell" would not be adequate).

Subgroup 5: Species of expressed double stranded RNA (e.g., see claim 76)

Applicant must elect, for the purposes of search, a ***single species*** of expressed double stranded RNA including whether said double stranded RNA consists of RNA alone or an RNA/DNA hybrid and, if so, which strands contain the DNA (e.g., see specification, page 21, last paragraph). Applicants must further indicate whether said dsRNA is a single molecule with an inverted repeat (see claim 82) or two strands bound to one another (e.g., see specification, page 21, last paragraph). Applicants must also indicate whether said double stranded RNA is transcribed from the same nucleic acid sequence

using two convergent promoters or is formed from two separate transcripts expressed from two promoters (e.g., see claims 83 and 84). Applicants must further indicate the total size of the dsRNA (i.e., give specific number, not just range). Applicants must further indicate whether said dsRNA is circular or linear (e.g., see specification, page 22). Applicants must further indicate whether said dsRNA has one or more modified nucleotides by specifying each and every change including whether the nucleotide contains a halogen, fluorine, methoxy group, etc (e.g., see specification, page 23, last paragraph).

Group II

10. If applicant elects the invention of Group II, applicant is required to elect from the following patentably distinct specie. Claim 104 is generic.

Subgroup 1: Species of monitoring cells for toxicity (e.g., see claims 104 and 108)

Applicant must elect, for the purposes of search, a ***single species*** of monitoring cells for signs of toxicity such as an RNA stress response like apoptosis. Other examples include measuring interferon induction 2'5' OAS activiation/induction, PKR induction/activation, anti-proliferative response, etc (e.g., see specification, page 36, last paragraph). Applicants must further elect a specific assay for monitoring the above phenotypes such as TUNEL assay, ELISA assay, etc. (e.g., see specification, page 36, last paragraph; see also claims 92, 93, 94, 95, 112, etc). Please be as specific as possible. Electing a general class will be held non-responsive. For example, electing detecting an RNA stress response using a microscope to look for one or more cytopathic effects (see claim 99) would be held non-responsive because the general class of cytopathic effects could be elected with greater specificity to include detached cells, rounded cells, etc (see claim 100). Likewise, electing the general class of apoptosis assay would be held to be non-responsive because this general class could be elected with greater specificity to cinlude Annexin V staining, propidium iodide staining, DNA laddering, etc (see claim 103).

Subgroup 2: Species of double stranded RNA (e.g., see claims 104 and 108)

Applicant must elect, for the purposes of search, a ***single species*** of expressed double stranded RNA including whether said double stranded RNA consists of RNA alone or an RNA/DNA hybrid and, if so, which strands contain the DNA (e.g., see specification, page 21, last paragraph). Applicants must further indicate whether said dsRNA is a single molecule with an inverted repeat (see claim 82) or two strands bound to one

another (e.g., see specification, page 21, last paragraph). Applicants must also indicate whether said double stranded RNA is transcribed from the same nucleic acid sequence using two convergent promoters or is formed from two separate transcripts expressed from two promoters (e.g., see claims 83 and 84). Applicants must further indicate the total size of the dsRNA (i.e., give specific number, not just range). Applicants must further indicate whether said dsRNA is circular or linear (e.g., see specification, page 22). Applicants must further indicate whether said dsRNA has one or more modified nucleotides by specifying each and every change including whether the nucleotide contains a halogen, fluorine, methoxy group, etc (e.g., see specification, page 23, last paragraph).

Subgroup 3: Species of positively charged delivery agent (e.g., see claims 104, 108)

Applicant must elect, for the purposes of search, a ***single species*** of charged delivery agent such as a cationic lipid, cationic surfactant, etc. Applicants must further elect a specific species with the broad class of lipid, surfactant, etc. In addition, Applicants must elect a specific ratio of delivery agent/dsRNA such as 5, 10, etc (i.e., please elect a specific number, not just a range like greater than 10 as set forth in claim 114).

Subgroup 4: Species of cells (e.g., see claim 104)

Applicant must elect, for the purposes of search, a ***single species*** of cell such as human cancer cell, stem cell, neuronal cell, etc. (e.g., see specification, page 8, paragraph 2). Please be a specific as possible (e.g., "human cell" would not be adequate).

Group III

11. If applicant elects the invention of Group I, applicant is required to elect from the following patentably distinct species. Claim 115 is generic.

Subgroup 1: Species of expressed double stranded RNA (e.g., see claims 115)

Applicant must elect, for the purposes of search, a ***single species*** of expressed double stranded RNA including whether said double stranded RNA consists of RNA alone or an RNA/DNA hybrid and, if so, which strands contain the DNA (e.g., see specification, page 21, last paragraph). Applicants must further indicate whether said dsRNA is a single molecule with an inverted repeat (see claim 82) or two strands bound to one another (e.g., see specification, page 21, last paragraph). Applicants must also indicate whether said double stranded RNA is transcribed from the same nucleic acid sequence using two convergent promoters or is formed from two separate transcripts expressed from two promoters (e.g., see claims 83 and 84). Applicants must further indicate the

total size of the dsRNA (i.e., give specific number, not just range). Applicants must further indicate whether said dsRNA is circular or linear (e.g., see specification, page 22). Applicants must further indicate whether said dsRNA has one or more modified nucleotides by specifying each and every change including whether the nucleotide contains a halogen, fluorine, methoxy group, etc (e.g., see specification, page 23, last paragraph).

Subgroup 2: Species of cells (e.g., see claim 115)

Applicant must elect, for the purposes of search, a ***single species*** of cell such as human cancer cell, stem cell, neuronal cell, etc. (e.g., see specification, page 8, paragraph 2). Please be a specific as possible (e.g., "human cell" would not be adequate). Applicants must also indicate whether said cells are cultured until no episomal vectors remain (see claim 116, 130, 131).

Subgroup 3: Species of dsRNA library (e.g., see claim 115)

Applicant must elect, for the purposes of search, a ***single species*** of dsRNA such as a cDNA expression library (see claim 127) and whether said dsRNA library is derived from a plurality of vectors (see claim 132). Applicants must also indicate whether said RNA expression library contains random sequences (see claim 128). Applicants must indicate whether said library is integrated randomly (see claim 117). Applicants must further elect the means by which said library is integrated (e.g., see claim 118 wherein the use of a retroviral expression library is disclosed). Applicants must further indicate whether said integration involves a loxP site in the presence of Cre recombinase (see claim 120). Applicants must further indicate the use of any and all promoter such as inducible promoters and, if so, elect a specific example (see claim 133 wherein various promoters are also listed). Applicants must also indicate whether the sense strand and the anti-sense strand of each double stranded RNA are transcribed from the same nucleic acid using two convergent promoters (see claim 134).

Subgroup 4: Species of modulation in biological activity (e.g., see claim 125)

Applicant must elect, for the purposes of search, a ***single species*** of modulation in cell activity including apoptosis, motility, cell invasion, etc (see claim 125). Applicants must further elect a specific assay for monitoring the above phenotypes such as TUNEL assay, ELISA assay, etc. (e.g., see specification, page 36, last paragraph; see also claims 92, 93, 94, 95, 112, etc). Please be as specific as possible (as noted above).

Subgroup 5: Species of identification (e.g., see claim 126)

Applicant must elect, for the purposes of search, a ***single species*** of identification such as by amplification and sequencing (see claim 126). Applicants must further indicate the amplification technique used such as PCR.

12. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be

considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
September 2, 2007

/Jon D. Epperson/
Primary Examiner, AU 1639